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☐ 1. Document ID: US 20060166894 A1

L17: Entry 1 of 1 File: PGPB Jul 27, 2006

PGPUB-DOCUMENT-NUMBER: 20060166894
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DOCUMENT-IDENTIFIER: US 20060166894 A1

TITLE: Ace-inhibitors having antioxidant and no-donor activity

PUBLICATION-DATE: July 27, 2006

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
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US-CL-CURRENT: 514/19; 514/149, 514/317, 514/424, 514/440, 514/616

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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Term	Documents
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(L11 AND L15).PGPB,USPT,USOC.	1

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L17: Entry 1 of 1 File: PGPB Jul 27, 2006

DOCUMENT-IDENTIFIER: US 20060166894 A1
TITLE: Ace-inhibitors having antioxidant and no-donor activity

Description of Disclosure:
[0050] The multifunctional ACE inhibitors compounds may also be employed in the treatment of conditions associated with endothelial dysfunction or oxidative stress including cardiovascular diseases (such as ischaemic heart disease, angina pectoris, myocardial infarction, congestive heart failure, atherosclerosis), diabetes mellitus, including the complications thereof (such as hypercholestemia, hypertension, atherosclerosis or Reaven's Syndrome, otherwise known as Syndrome-X), endothelial dysfunction-induced diseases, insulin-resistance and glucose intolerance in diabetes, ischemia-reperfusion tissue injury, peripheral vascular disease, critical limb ischemia, arterial aneurysms, microvascular diseases, hypertension (e.g., pulmonary, systemic, ocular, obesity or pregnancy-induced), management of arrhythmia (including but not limited to supraventricular arrhythmias, atrial tachycardia) and drug or disease induced nephropathy (e.g. diabetic nephropathy).

Description of Disclosure:
[0062] In particular, described herein are nitrosated or nitrosylated ACE inhibitor agents possessing SOD-mimic and/or ROS scavenger components, which ACE inhibitors are optionally substituted with at least one ONO, SNO, or ONO.sub.2 moiety, or a compound that donates, transfers, or releases nitric oxide in either a neutral or a charged form.

Description of Disclosure:
[0115] In particular, the invention relates to nitrosated or nitrosylated ACE inhibitor agents with SOD-mimic/Anti-ROS actions which can optionally be substituted with at least one ONO, SNO, or ONO.sub.2 moiety, or a compound that donates, transfers, or releases nitric oxide in either a neutral or a charged form.

Description of Disclosure:
[0189] The multifunctional ACE inhibitor compounds may also be employed in the treatment of conditions associated with endothelial dysfunction or oxidative stress including cardiovascular diseases (such as ischaemic heart disease, angina pectoris, myocardial infarction, congestive heart failure, atherosclerosis, hypertension (e.g., pulmonary, systemic, ocular, obesity or pregnancy-induced), and management of arrhythmia (including but not limited to supraventricular arrhythmias, atrial tachycardia).

CLAIMS:

66. A method according to claim 49, wherein said disorder is selected from the group consisting of ischaemic heart disease, angina pectoris, myocardial infarction, congestive heart failure, cardiomyopathy, atherosclerosis, ischaemia-reperfusion tissue injury, peripheral vascular disease, critical limb ischaemia, palpitations, arrhythmia, tachycardia, sinus, thyrotoxicosis, pheochromocytoma,

tension, anxiety, alcohol withdrawal, anxiety, migraine, arterial aneurysm, microvascular diseases, hypertension selected from pulmonary-, systemic-, ocular-, obesity-, and pregnancy-induced, impotence, diabetes mellitus, hypercholestemia, Reaven's syndrome, diabetic nephropathy, insulin-resistance and glucose intolerance in diabetes, endothelial dysfunction or oxidative stress-induced diseases, drug or disease induced nephropathy, and esophageal varices.

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L17: Entry 1 of 1 File: PGPB Jul 27, 2006

PGPUB-DOCUMENT-NUMBER: 20060166894
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20060166894 A1

TITLE: Ace-inhibitors having antioxidant and no-donor activity

PUBLICATION-DATE: July 27, 2006

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Haj-Yehia; Abdullah Ibrahim	Neve Shalom	CA	IL
Khan; Mohamed Amin	Morgan Hill		US
Qadri; Bashir Ali	Kfar Nahif		IL

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	COUNTRY	TYPE CODE
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APPL-NO: 10/536628 [PALM]
DATE FILED: November 27, 2003

RELATED-US-APPL-DATA:
us-provisional-application US 60429864 20021129
us-provisional-application US 60430003 20021129

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Nov 27, 2003	PCT/IL03/01006			Dec 19, 2005

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CIPS	A61 K 31/16	20060101
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US-CL-CURRENT: 514/19; 514/149, 514/317, 514/424, 514/440, 514/616

ABSTRACT:

Multifonctional ACE inhibitor compounds are provided, that combine ACE-inhibiting activity with capability to scavenge superoxide and other reactive oxygen species, and that may further function as nitric oxide donors. The compounds are useful for preventing or treating various disorders, including cardiovascular, and diabetes associated disorders.

TECHNICAL FIELD

[0001] The present invention relates to multifunctional ACE (angiotensin converting enzyme) inhibitor compounds that are capable of, in addition to inhibiting ACE, scavenging superoxide or other reactive oxygen species, and optionally also acting as NO-donors. The invention further relates to methods of using such compounds in the treatment of various pathological conditions.

BACKGROUND OF THE INVENTION

[0002] Hypertension is a major disorder affecting the populations of developed countries. The pathology of hypertension is multifactorial and in cases of inappropriate or inadequate treatment can lead to heart disease and/or injury to organs such as the kidneys, blood vessels, eyes and other vital systems [Amery A. et al.: Lancet 1 (1985) 1349-54].

[0003] There is much evidence to support a relationship between the development and pathology of hypertension and oxidative stress--an imbalance between the production of reactive oxygen species (ROS) and the endogenous mechanisms for protecting against ROS, including antioxidant enzymes like superoxide dismutase (SOD), glutathione peroxidase, glutathione reductase, catalase and low molecular weight antioxidants like vitamin C, vitamin E and glutathione [Ames B. N. et al.: Proc. Natl. Acad. Sci. USA. 90 (1993) 7915-22].

[0004] Hypertension usually accompanies other diseases related to oxidative-stress, such as diabetes, atherosclerosis, cancer and also diseases known to be related to overproduction of ROS such as alcoholism, smoking and morbid obesity.

[0005] Recent research suggests that a direct relationship exists between hypertension and states of oxidative stress, depletion of antioxidant capacity, accelerated cell ageing and depletion of cellular energy. This theory is based on mechanisms thought to underlie the pathology of hypertension such as elevated oxidative injury, increased fibrogenesis, inhibition of Na.sup.+--K.sup.+ ATPase pump activity and cardiac hypertrophy. Existing therapy for hypertension includes vasodilators and other blood pressure reducing agents that can reduce mortality due to heart failure and slow the development of other complications of hypertension.

[0006] Angiotensin converting enzyme (ACE) inhibitors constitute a cornerstone in the treatment of hypertension and in vascular protection. The first ACE inhibitor (ACEI), captopril, was described in 1977, and other recently developed ACEI can act

on the crucial enzyme that generates the potent vasoconstrictor--angiotensin II (Ag-II)--from angiotensin I (Ag-I) [Opie L. H.: Drugs for the heart, 5th ed. (2001) pp 107-15.3].

[0007] Angiotensin converting enzyme (ACE) is a peptidylcarboxypeptidase, which catalyzes the cleavage of dipeptides at the carboxy terminal. ACE is responsible for the conversion of Ag-I to Ag-II and for the deactivation of bradykinin (hence the alternative name Kininase). Ag-II is a peptide that promotes blood vessel contraction and thus blood pressure elevation. Deactivatation of bradykinin, a peptide that induces smooth muscle relaxation, is another way in which ACE is thought to elevate blood pressure. ACE inhibition is therefore vasodilatory due to the decreased formation of angiotensin II, and potentially due to the increased bradykinin activity.

[0008] Human ACE consists of 1278 amino acids, forming two homologue domains. Each homologous domain contains two main sites: catalytic and binding. The enzyme occurs in all vascular beds but it is chiefly found in the vascular endothelium of the lungs [Garison J. C. and Peach M. J.: Cardiovascular Drugs, In: Goodman and Gillman's: The Pharmacological Basis of Therapeutics, Goodman A. G., Rall T. W., Nies A. S., Taylor P. editors., 8.sup.th ed. Pergamon Press, USA. p. 752 (1990)].

[0009] The structure of the enzyme was extensively studied in efforts to explain the structure-activity relationship of enzyme inhibitors isolated from the venom of Bothrops jacaraca and their synthetic analogues. In one proposed model, the enzyme is divided into two main domains: obligatory ("oblig.bind.") and auxiliary ("aux.bind.") (FIG. 1). Both substrates ("subst.") and inhibitors bind to the enzyme catalytic site in the same manner, which involves attachment to a number of specific binding sites. Spectroscopic tests have shown that the binding site of the enzyme contains a zinc ion. This binding site is considered as a key target for the development of the new nonpeptide inhibitors of the ACE. The natural enzyme substrates and peptide inhibitors do not usually bind to the positively charged zinc ion, while nonpeptide inhibitors do.

[0010] According to the model proposed for ACE inhibition [Ondetti M. A.: Circulation 77 (supp I) (1988) I74-I78], the structural requirements for an effective inhibitor are a carboxylic acid or ester group at one side of the molecule, a carbonyl, or preferably, an amide group, a methyl group in an alpha position to the carbonyl group, a group that can bind to the zinc ion, and the presence of pyrrolidine in the carboxylic side chain.

[0011] Investigations into the ACE inhibitor binding site led to the synthesis of potent new non-peptide ACE inhibitors, such as Captopril and Enalapril (FIG. 2).

[0012] Binding of Ag-II to its receptor induces smooth muscle contraction via a complex signalling pathway. The pathway starts with phospholipase C stimulation causing breakdown of phosphatidylinositol bisphosphate to inositoltriphosphate (IP.sub.3) and diacylglycerol. IP.sub.3 liberates calcium from intracellular store, such as the sarcoplasmic reticulum, to stimulate muscular contraction and hence vasoconstriction. Diacylglycerol activates protein kinase C, which transfers phosphate from adenosine triphosphate (ATP) to a target protein leading to the stimulation of proto-oncogenes.

[0013] Activation of protein kinase C through ligation of Ag-II receptors is thought to promote ventricular hypertrophy. Furthermore, ligation of Ag-II receptors can induce the activation of NADPH oxidase via a signal transduction involving protein kinase C and other molecules. Activation of NADPH oxidase leads to the generation of superoxide anions [Griendling, K. K. et al.: Circ. Res. 74 (1994) 1141-48; Rajagopalan, S. et al.: J. Clin. Invest. 97 (1996) 1916-23]. It is

believed that production of superoxide anions following activation of angiotensin II receptors contributes to the biological effects of angiotensin. Rajagopalan [Ibid.] found that angiotensin II induces elevation of blood pressure accompanied with a remarkable elevation in superoxide together with a decrease in the release of endothelial nitric oxide (NO). This increase in superoxide levels did not occur when the elevation of blood pressure was induced by norepinephrine. On the other hand, there was no elevation of the blood pressure after adding the superoxide dismutase (SOD) enzyme together with angiotensin II, while the addition of SOD to norepinephrine did not prevent the elevation in blood pressure. These results indicate that angiotensin induces elevation of blood pressure through elevation of endogenous superoxide free radicals [Rajagopalan, Ibid.]. Therefore, scavenging superoxide anions at the site of angiotensin action, could lead to a reduced response to angiotensin.

[0014] The production of free radicals in the vascular system by angiotensin II seems to have a major rule in the development of hypertension and other cardiovascular diseases related to the renin-angiotensin system. Recent studies indicate the importance of supplementary antioxidants together with smooth muscle relaxant for the treatment of hypertension in order to prevent the pathological development of hypertension and other cardiac diseases.

[0015] Supplementation of exogenous antioxidants in these conditions may prevent tissue damage and the progress of the disease but it does not seem to be a solution, as external administration of antioxidants cannot restore the antioxidant capacity in the injured tissue.

[0016] In recent published research concerning the antioxidant activity of the different available ACEI, it was found that the sulfhydryl containing ACEI have better antioxidant activity than other ACEI's, due to the ability of the thiol group to quench reactive oxygen species [Bartosz M.: Free Radical Biology and Medicine 23 (1997) 729-35; Mak I. T.: Biochem. Pharmacol. 40 (1990) 2169-75].

[0017] The endothelial derived relaxing factor nitric oxide (NO) has a great importance in regulating the circulatory system and blood pressure besides other important systems in the body. It is produced in the body by a variety of tissues such as the nervous system, muscles, liver and the immune system. NO-donors can be used clinically for the treatment of cases where depletion of NO is observed such as ischemic heart disease. Unfortunately, existing NO-donors are known to elicit development of resistance and their efficacy is limited. The major problem arises from the fact that high levels of NO together with elevated levels of superoxide may lead to the production of peroxynitrite which is another potent free radical species, and can effect severe tissue damage [Munzel T. J: Clin. Invest. 95 (1995) 187-94]. Recent evidence shows that, in vascular complications of diabetes, it is peroxynitrite rather than NO itself that is responsible for the vascular disorders. Indeed, peroxynitrite is one hundred times more potent than NO in causing some of the detrimental effects originally attributed to NO, such as inhibition of cellular respiration through inactivation of critical mitochondrial enzymes.

[0018] NO is formed from the amino acid L-arginine by several forms of NO synthases, and plays a role in a number of physiological functions, including the relaxation of airway smooth muscle. NO formed in endothelial cells in response to chemical agonists and to physical stimuli plays a key role in regulation of vascular tone, platelet aggregation and adhesion, as well as modulating smooth muscle proliferation [Haj-Yehia A. et al.: Drug. Development Res. 50 (2000) 528-36]. NO overproduction has also been associated with numerous disease states (WO 99/66918).

[0019] Publications disclosing nitric oxide donor compounds or compounds which

promote the synthesis of nitric oxide include WO 98/42661, WO 99/37616, WO 00/31060, WO 97/34871, WO 00/35434, WO 99/62509, WO 97/25984, WO 00/67754, WO 9961018, WO 99/61430, WO 97/31654, WO 96/32946, WO 00/53191, U.S. Pat. Nos. 6,248,895 and 6,232,331 and Wolf et al.: J. Neurosurg. 89 (1998) 279-88. Publications disclosing nitric oxide scavenger compounds include WO 98/55453.

[0020] The endothelium, in addition to producing NO, also produces superoxide (SO) anion and other reactive oxygen species (ROS) under physiological conditions. Despite SO being a reducing agent that is itself incapable of initiating oxidative reactions, SO is considered the most important source of oxidative stress. Compounds for the removal of SO are described in the art, including WO 96/39409 and U.K. Pat. App. No. 2349385A.

[0021] Many disease states, including diabetes mellitus and various cardiovascular diseases, are associated with oxidative stress and endothelial dysfunction. Nitroglycerin (GTN) has been used for the treatment of various types of myocardial ischemia. Because of its pathogenic nature (chronicity with acute exacerbation), prophylactic and acute treatments are necessary to prevent complications with potentially fatal outcomes (>25% death for acute MI). However, the phenomenon of tolerance to the anti-anginal effects of GTN and to all other existing organic nitrates is of a special clinical significance. In particular, early development of tolerance to the drug is by far the most serious drawback of nitrate therapy.

[0022] A number of cardiovascular conditions have been recognized, (e.g., angina, hypertension, arrhythmias, congestive heart failure) and a number of other conditions (e.g., migraine, tachycardia such as sinus, pheochromocytoma, thyrotoxicosis, tension, anxiety, and the symptoms of hyperthyroidism) have been recognized, many of which have overlapping and interacting etiologies.

[0023] Various compounds and treatments for cardiovascular conditions are disclosed in the art, for example, in U.S. Pat. Nos. 6,444,702, 6,417,207, 6,255,296, 6,051,571, 6,440,961, 6,429,219, 6,423,724, and 6,248,895.

[0024] Similarly, compounds and treatments for migraines are disclosed in the art, for example, U.S. Pat. Nos. 6,458,840, 6,458, 830, 6,444,702, 6,376,550, 6,414,505, 6,403,627, 6,355,689, 6331,553, 6,265,441, 6,423,724, and 6,455,549.

[0025] Various compounds and treatments for sinus tachycardia are disclosed in the art, for example, U.S. Pat. No. 6,100,297.

[0026] Compounds and treatments for hypertension are disclosed in the art, for example, U.S. Pat. Nos. 6,440,961, 6,429,219, 6,423,724, 6,214,817, and 6,455,542.

[0027] Various compounds and treatments for the symptoms of hyperthyroidism are also disclosed in the art, for example, U.S. Pat. Nos. 6,110,959, 6,121,309, and 6,437,165.

[0028] ACE inhibitors are useful in the treatment of hypertension. Inhibition of ACE lowers systemic vascular resistance and mean, diastolic and systolic blood pressures in various hypertensive states. The effects are readily observed in animal models of renal and generic hypertension. In humans subjects with hypertension, ACE inhibitors commonly lower blood pressure (except when due to primary aldolsteronism).

[0029] ACE inhibitors alone normalize blood pressure in approximately 50% of patients with mild to moderate hypertension, and many consider ACE inhibitors first-line drugs for the treatment of high blood pressure. About 90% of patients

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☐ 1. Document ID: US 20060009513 A1

L10: Entry 1 of 6 File: PGPB Jan 12, 2006

PGPUB-DOCUMENT-NUMBER: 20060009513
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20060009513 A1

TITLE: Nebivolol and its metabolites in combination with nitric oxide donors, compositions and methods of use

PUBLICATION-DATE: January 12, 2006

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Garvey; David S.	Dover	MA	US

US-CL-CURRENT: 514/459; 549/330

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 2. Document ID: US 20040132805 A1

L10: Entry 2 of 6 File: PGPB Jul 8, 2004

PGPUB-DOCUMENT-NUMBER: 20040132805
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040132805 A1

TITLE: Nitrosated and nitrosylated nebivolol and its metabolites, compositions and methods of use

PUBLICATION-DATE: July 8, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Garvey, David S.	Dover	MA	US

US-CL-CURRENT: 514/456; 549/398

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

L10: Entry 5 of 6 File: PGPB Jan 8, 2004

PGPUB-DOCUMENT-NUMBER: 20040005306
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040005306 A1

TITLE: Methods of treating vascular diseases characterized by nitric oxide insufficiency

PUBLICATION-DATE: January 8, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
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Loberg, Michael D	Boston	MA	US
Morce, Manuel	Boston	MA	US

US-CL-CURRENT: 424/94.1; 424/468, 424/94.4, 514/18, 514/248, 514/458, 514/474, 514/509, 514/562, 514/683

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 6. Document ID: US 7138430 B2

L10: Entry 6 of 6 File: USPT Nov 21, 2006

US-PAT-NO: 7138430
DOCUMENT-IDENTIFIER: US 7138430 B2

TITLE: Nitrosated and nitrosylated nebivolol and its metabolites, compositions and methods of use

DATE-ISSUED: November 21, 2006

PRIOR-PUBLICATION:

DOC-ID	DATE
US 20040132805 A1	July 8, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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US-CL-CURRENT: 514/456; 549/401, 549/407

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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